MODULE III:

Risks Factors & Genetics

Risk Factors

Breast Cancer

- Will affect 1 in 8 women by the age of 85
- Every 3 minutes another woman is diagnosed with breast cancer

Risk Factors for Breast Cancer

- Personal history of breast cancer
  - Risk for a contralateral cancer is 0.7% per year
- Atypical hyperplasia, LCIS, or DCIS
- Estrogen exposure
  - First menstrual period before age 12
  - First birth after age 30 or nulliparity
  - Late menopause (after age 50)
  - Postmenopausal ERT or HRT

Risk Factors for Breast Cancer

- Too little exercise
- Alcohol consumption
- Weight gain
- High-dose radiation exposure to chest
  - Hodgkin’s Disease
- Smoking
- Diet?

Risk Factors for Breast Cancer

- Breast Density, as seen on mammogram
- Blood levels of sex hormones

Risk Factor: Age

By Age 25..... 1 in 19,608
By Age 30..... 1 in 2,525
By Age 35..... 1 in 622
By Age 40..... 1 in 217
By Age 45..... 1 in 93
By Age 50..... 1 in 50
By Age 55..... 1 in 33
By Age 60..... 1 in 24
By Age 65..... 1 in 17
By Age 70..... 1 in 14
By Age 75..... 1 in 11
By Age 80..... 1 in 9
Ever..... 1 in 8

Risk Factors: Family History

First-Degree Relatives ——— **RR 2.3**

Second-Degree Relatives ——— **RR 1.5**

Both Mother and Sister Affected ——— **RR 14.0**

Satlin, et. al., JAMA 253:1985

Risk Factors: Family History

First-degree Relative	RR
NO HISTORY	1.0
Unilateral/Postmenopausal	1.2
Unilateral/Premenopausal	1.8
Bilateral/Postmenopausal	4.0
Bilateral/Premenopausal	8.8

Risk: Age at First Birth

AGE	RR
<20	1.0
20-24	1.2
25-29	1.6
30-35	1.9
35+	2.4
NULLIP	2.0

MacMahon, et.al., 1970

Breast Cancer Risks

Proliferative benign breast disease on biopsy

Risk Factor	**Relative Risk**
Atypical hyperplasia	4
Atypical hyperplasia & family hx	11

Hormone Replacement

- Relative risk of breast cancer increases with each year of HRT use
- Risk of breast cancer increases 35% after using HRT for 5 or more years
- Cancers diagnosed in ever-users were less advanced clinically than those in never users
- The cumulative excess number of breast cancers per 1000 women are 2, 6, and 12 for durations of 5, 10, and 15 years, respectively

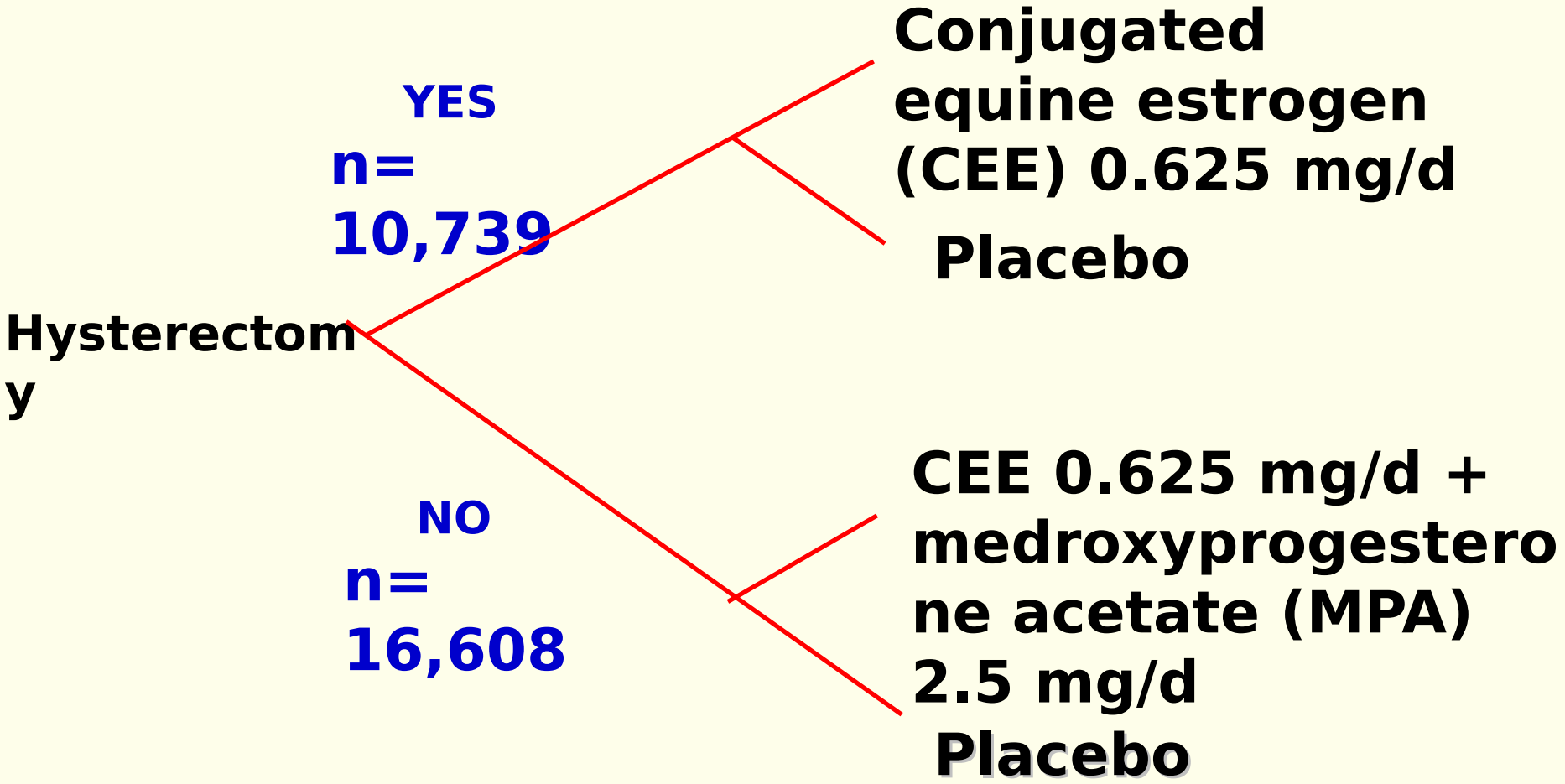
Collaborative Group on Hormonal Factors in Breast Cancer.
Lancet 350:1047-59, 1997

Women's Health Initiative

- HRT vs. identical placebo
- enrolled 27,500
- assesses the effect of HRT in the incidence of cardiovascular disease, breast cancer and osteoporosis
- Estrogen + progestin vs. placebo given to 16,608 postmenopausal women with an intact uterus

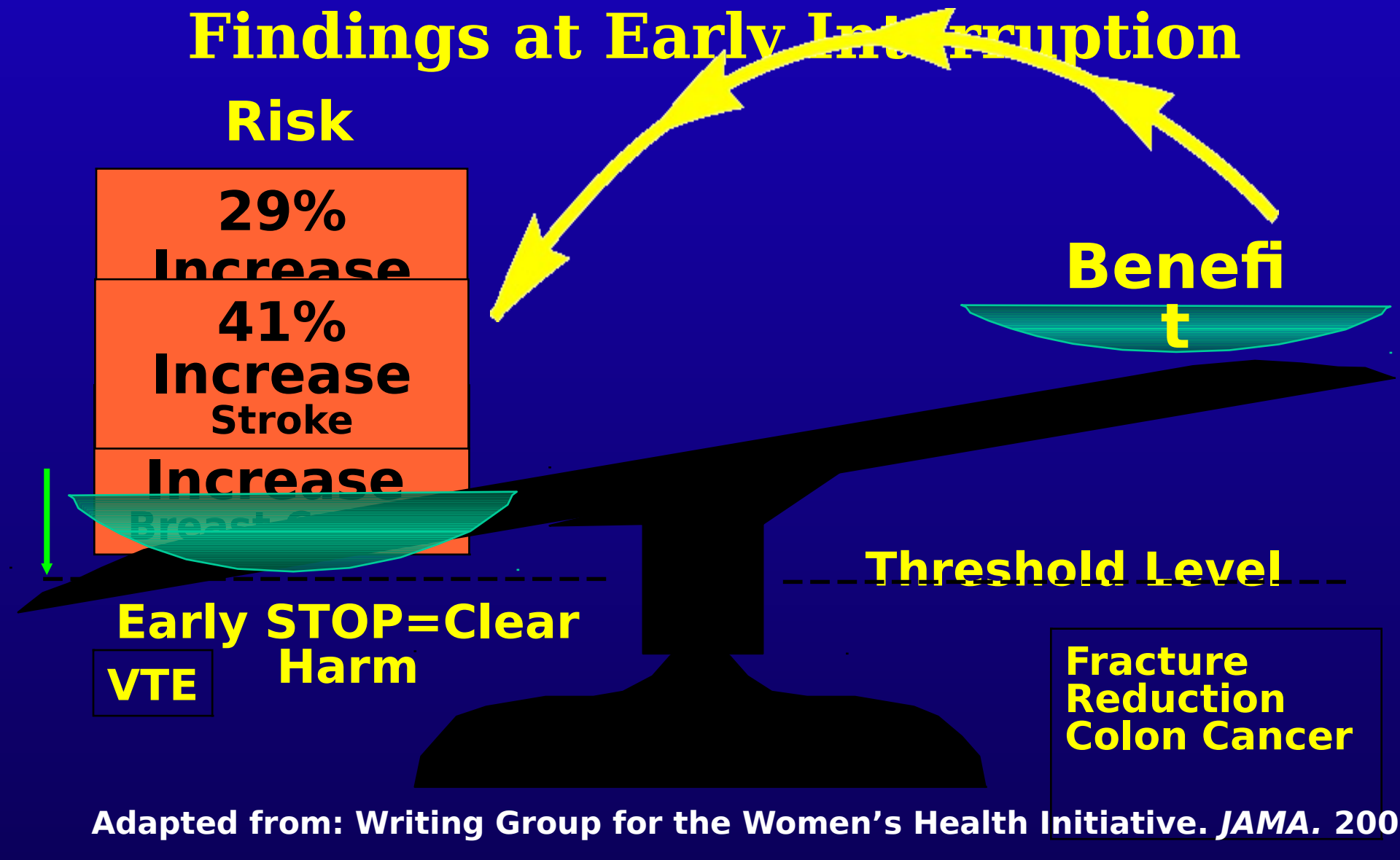
Writing Group for WHI. JAMA 2002;288:321-333

WHI Hormone Program Design



Women's Health Initiative

Findings at Early Interruption



Adapted from: Writing Group for the Women's Health Initiative. *JAMA*. 200

Relative increase in event rates per 10,000 women at 5.1 years of follow-up in the WHI

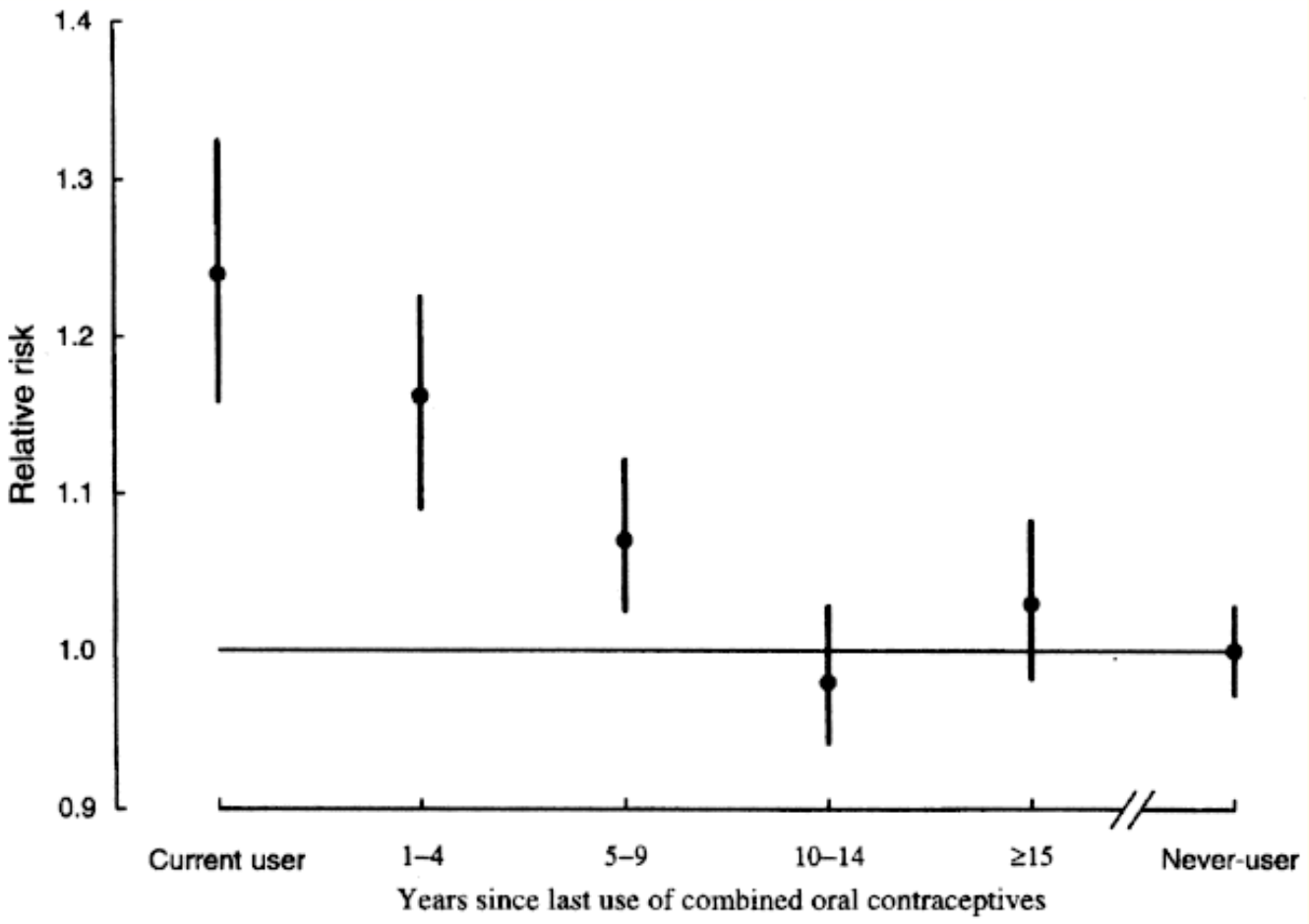
- 26% increase in breast cancer (38 vs. 30)
- 41% increase in strokes (29 vs. 21)
- 29% increase in heart attacks (37 vs. 30)
- Doubled rates of DVT and PE (34 vs. 16)
- 37% less colorectal cancer (10 vs. 16)
- 34% fewer hip fractures and 24% less total fractures (10 vs. 15 and 147 vs. 191)

Writing Group for WHI. JAMA 2002;288:321-333

Risk of Breast Cancer with OCP Use

- If there is an increase in the risk of breast cancer with OCP use, it is small
- OCP use may reduce the risk of ovarian cancer
- U of Toronto study showed an increase risk of breast cancer in OCP users with a BRCA1 mutation

Relative risk of breast cancer time since last use of OCP

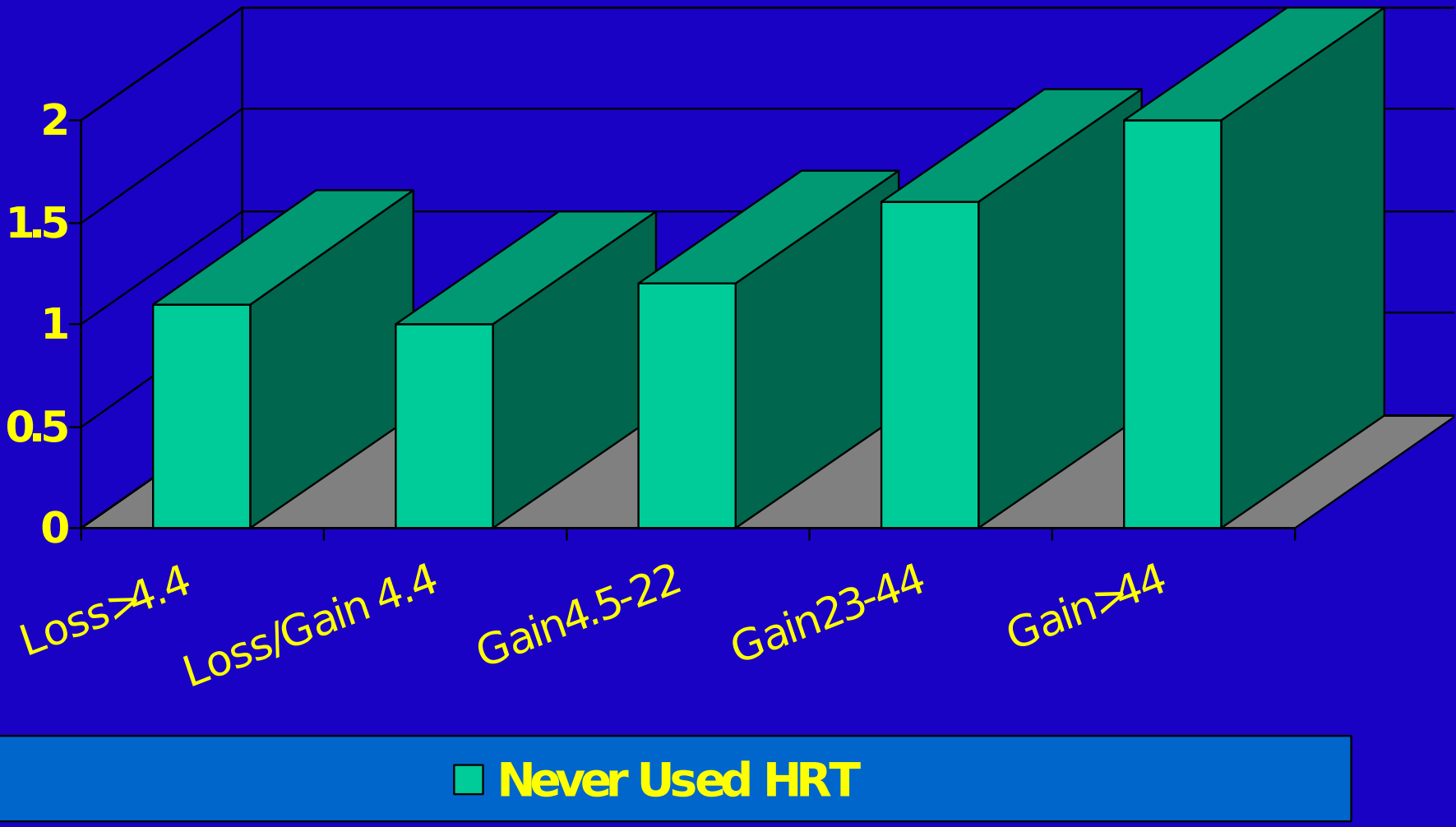


Collaborative Group on Hormonal Factors in Breast Cancer.

Obesity

- Obese women have higher estrogen levels
- Increased waist circumference is associated with an increased risk of breast cancer, 36 to 55 inches have a relative risk of 1.88
- Central obesity is associated with increased bioavailability of estradiol

Relative Risk of Breast Cancer Related to Adult Weight Change



Weight Gain Affects Prognosis

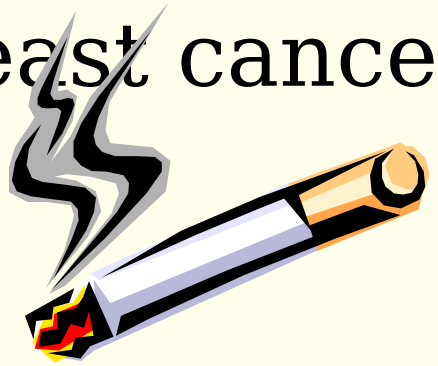
Women with breast cancer who are overweight or gain weight after diagnosis are found to be at greater risk for breast cancer recurrence and death compared with lighter women

Chlebowski, et al. J Clin Onc 20;1128-1143;2002

Smoking

- Smokers experience up to a 4.4 times greater risk of developing breast cancer

- Persons with a slow metabolism rate for the enzyme N-Acetyltransferase-2 have a significant risk of breast cancer related to smoking

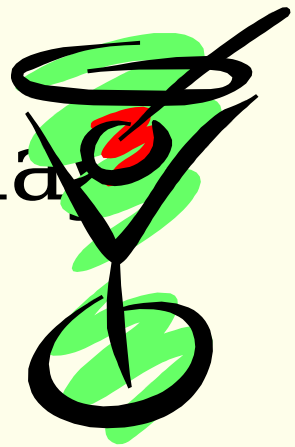


Alcohol

A woman's risk of breast cancer more

than doubles when she has two or

more alcoholic drinks per day.



Diet

- Incidence of breast cancer is much lower in Japan, Thailand, Nigeria, and India than in Denmark, the Netherlands, New Zealand, Switzerland, the UK and US
- These trends in breast cancer incidence may be related to dietary influences, particularly dietary fat consumption

Estradiol Levels

- Women with the highest levels of estradiol and free estradiol had a RR of breast cancer of 2.0 and 2.58, compared to women with the lowest levels of these hormones

- Measuring sex hormone levels to assess an individual's risk of future breast cancer, is not current practice

JNCI
2002:94:606

Breast Cancer Risks

No increased risk of breast cancer risk:

- **Breast augmentation**
- **Pregnancy loss or termination**

Risk Factors

75% of Women Diagnosed With Breast Cancer Have No Known Risks Other Than Age and Gender

The single most important risk factor for the development of breast cancer is

Every
woman
is at risk for
breast
cancer.

BREAST CANCER RISKS

THE GOOD NEWS!

Lactation and Breast Cancer Risk

- Lactation seems to reduce breast cancer risk by 25-30%
- Studies have shown that women who breastfed have a 25% reduction in breast cancer

Exercise and Breast Cancer

- Over 20 published studies evaluating physical activity and the risk of breast cancer
  - Majority showed clear evidence of a lower risk for breast cancer in exercising women
  - Reduction in risk was 10-70% for the most active women and 30-40% for women exercising 3-4 hours per week
  - Lower risk observed for both premenopausal and postmenopausal breast cancer

McTiernan, A. The Oncologist 2003;8:326
Thune I. Med Sci Sports Exerc 2001;33:S530

Lifestyle Recommendations

- Maintain ideal body weight
- Moderate exercise (3-4 per week)
- Limit alcohol consumption

Breast Cancer Risk Assessment Tool

- Each of the major risk factors can be put into a mathematical equation that predicts a woman's risk of breast cancer in the next five years
- *Gail Model:* **http://bcra.nci.nih.gov/brc/**

High Risk for Breast Cancer

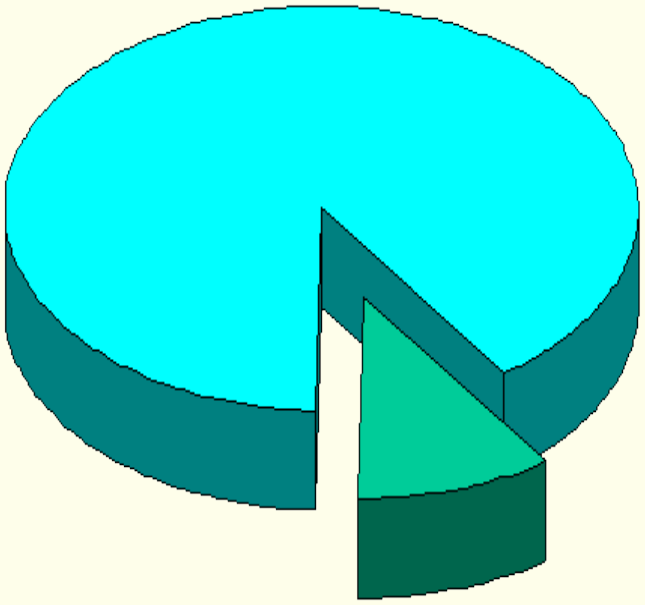
Gail Risk Assessment

[No h/o breast cancer]

>1.66% 5 year risk invasive breast cancer

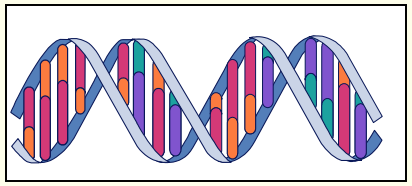
Genetics

How Much Breast Cancer Is Hereditary?

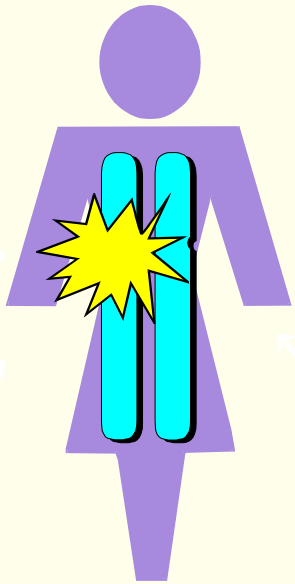


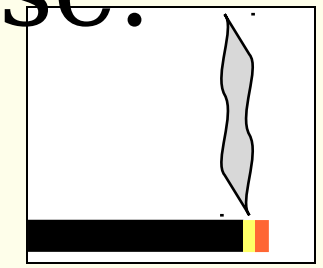
5%–10%

Factors affecting whether a person with a mutation will develop the disease:



Modifier genes





Carcinogens

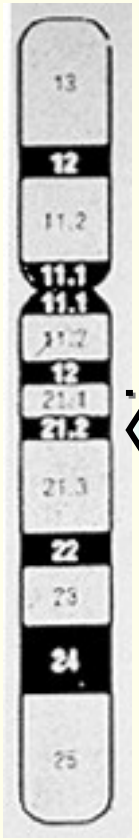
Response to DNA damage

Hormonal/ reproductiv e factors

Not everyone with an altered gene develops cancer

BRCA Gene

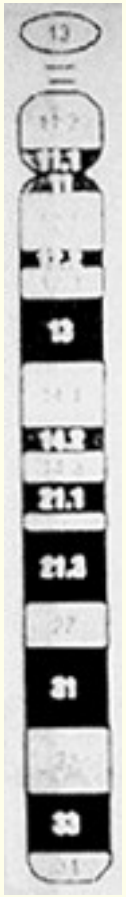
Chromosome 17



BRCA-1 gene

- **Discovered in 1990**
- **Isolated in 1994**
- **About $^1/_3$ of HBC**
- **Breast and breast-ovary HBC**
- **No male breast cancer members**
- **Over 3400 different mutations reported**

Chromosome 13



BRCA-2 gene

- **Discovered in 1994**
- **Isolated in 1995**
- **About $^1/_3$ of HBC**
- **HBC with male breast cancer members**
- **Less ovarian cancer than with BRCA-1**
- **Over 2000 different mutation reported**

BRCA - Autosomal Dominant

Normal Father

Affected Mother

Normal Female

Affected Female

Affected Male

Normal Male

BRCA1 – Lifetime Risk

Primary Female Breast Cancer

- 35% - 85%

Second Breast Cancer

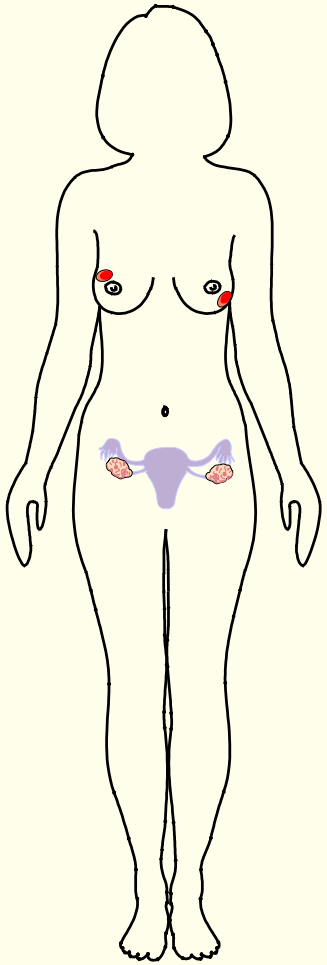
- 50% risk

Ovarian Cancer

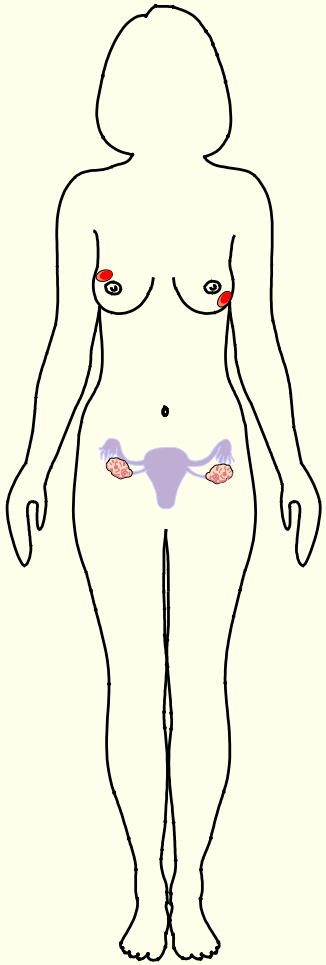
- Up to 60%

Male Breast Cancer

- Small increased risk with BRCA1



BRCA2 – Lifetime Risk



Primary Female Breast Cancer

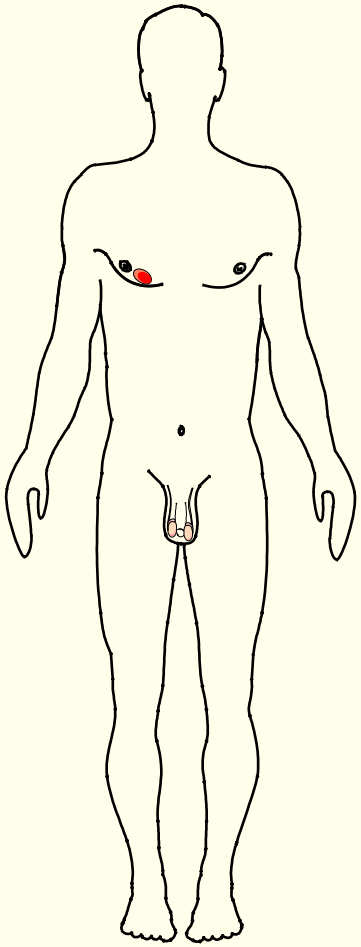
- Many studies find lower risks with BRCA2 mutations compared with BRCA1

Ovarian Cancer

- Up to 30%

Male Breast Cancer

- 6% lifetime risk with BRCA2



BRCA – Lifetime Risk, cont.

Prostate Cancer

- Up to a 3-fold increased risk for BRCA1 and possibly with BRCA2

Melanoma

- Increased risk with BRCA2 mutations.

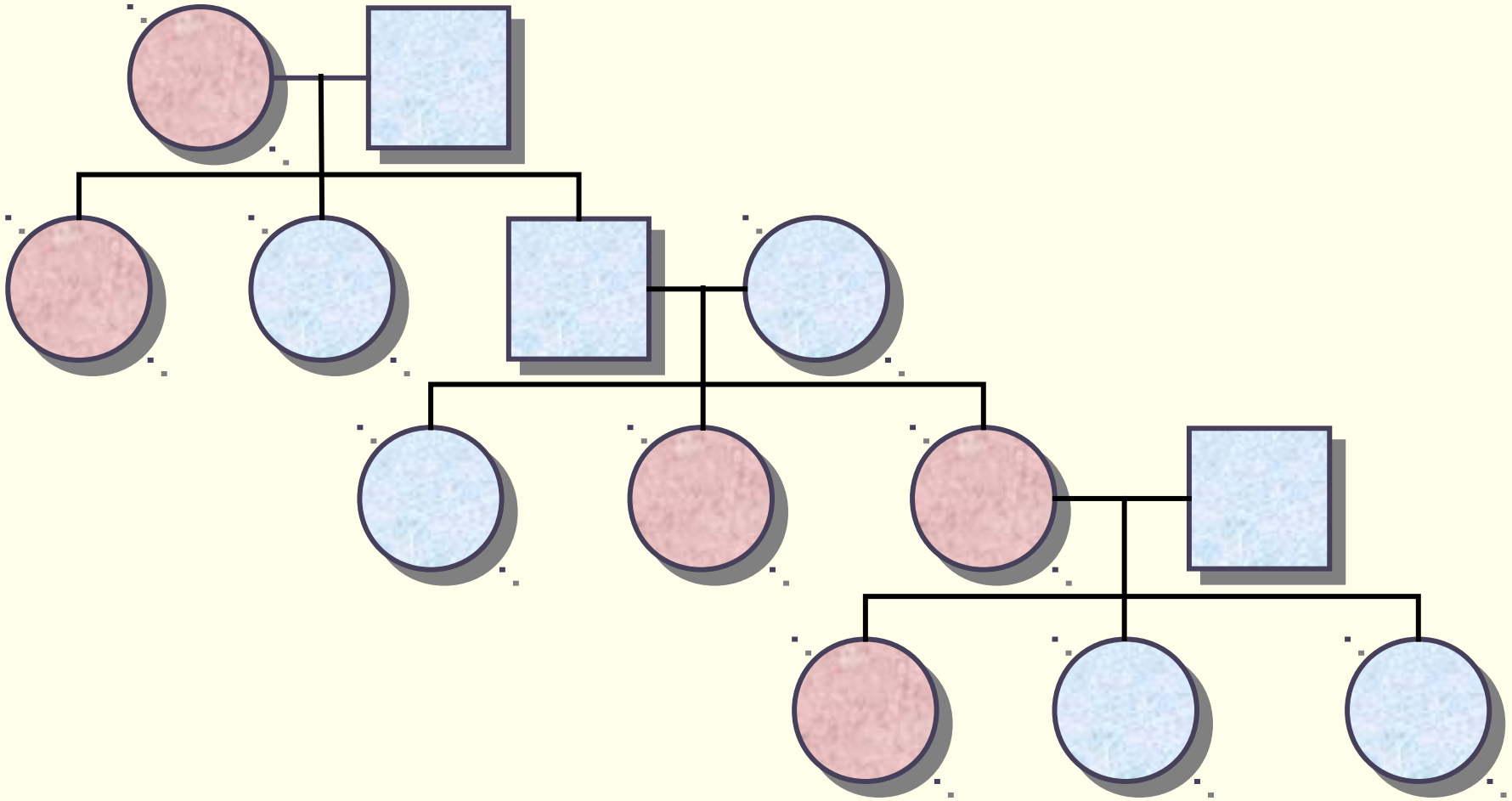
Pancreatic Cancer

- Increased risk with BRCA2 mutations.

Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer in the family
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Ashkenazi Jewish heritage
- Male breast cancer
- Blood relatives of those who carry a BRCA-1 or BRCA-2 mutation (applicable to men or women)

Genetic Testing for Breast and Ovarian Cancer



Genetic Testing

For affected patients:

- Information about future cancer risks
- Information to guide preventative treatment decisions
- Useful for children and other relatives

For unaffected family members:

- Information about specific future cancer risks
- Reduction in uncertainty

Inherited Genetic Mutations in Breast Cancer

Issues:

- Counseling both pre- and post-test
- Mechanisms for confidentiality
- Life insurance
- Health insurance
- Employability
- Minors

Genetic Testing for Breast and Ovarian Cancer

Pre-Test Counseling

- Risks and benefits of testing
- Efficacy and limitations of testing
- Chance of disease
- Confidentiality of results
- Legal, ethical, and psychological implications of testing
- Psychological support availability
- Recommendations based on results
- Availability of medical services

Genetic Testing Outcomes

- Choose not to be tested or don’t want results
- Genetic mutation identified
- No mutation identified
- Mutation of unclear significance

Management Options

- Surveillance
- Chemoprevention
- Prophylactic mastectomy
- Prophylactic oophorectomy

Surveillance

Breast Cancer Prevention:

- Frequent breast self and clinical exams
- Mammography
  - Start earlier (20-30s for known mutation carriers)
- Breast Ultrasound?
- Breast MRI?
  - Higher sensitivity than mammography, but with false positives
  - Expensive
- PET? (Clinical trials underway)

Ovarian Cancer Prevention:

- Annual or biannual clinical pelvic exam
- Transvaginal ultrasound with Doppler flow imagery
- Annual or biannual CA-125 measurement

Chemoprevention

Breast Cancer Prevention:

- Tamoxifen
  - Utility for BRCA1 carriers uncertain
  - Most BRCA1 tumors are estrogen receptor negative
- Arimidex?
- Raloxifene?

Ovarian Cancer Prevention:

- Oral contraceptives
  - Appears to reduce risk for ovarian cancer in BRCA carriers
  - May increase risk for breast cancer

Prophylactic Surgery Issues

- Quality of life
  - Body image, self-esteem
  - Loss of nipple sensitivity
- Residual cancer risk
- Decision must be individualized

Prophylactic Surgery

Comparison of Life Expectancy Gains:

- PCM 0.6-2.1 years
- PO 0.2-1.8 years

(Schrag et al, JAMA 2000)

Prophylactic Mastectomy

- Reduces breast cancer risk by 90%
- All studies are retrospective

Prophylactic Mastectomy

	Ziegler	Jarrett	Pennisi	Woods	Hartmann
#patients	285	100	1500	1400	1040
% high risk	6%	NS	49%	NS	21%
Surgery	Subq	Simple	Subq	Subq	Subq-89% Simple-11
#with cancer	3	0	6	3	7

Prophylactic Mastectomy, cont.

Group	N	Breast Cancers (%)
High risk women with mastectomy	214	3 (1.4)
Their sisters with no mastectomy	403	156 (38.7)

Hartmann et al. N Engl J Med 1999;340:77-84.

Prophylactic Oophorectomy

- Significantly reduces the risk of ovarian cancer, although there is still a residual risk for primary peritoneal cancer
  - Prevention and Observation of Surgical Endpoints (PROSE) study group
    - 96% reduction in ovarian cancer risk
    - 53% reduction in breast cancer risk
- Prophylactic hysterectomy
    - Remove the fallopian tubes completely
    - Controversial (No evidence of uterine cancer risk)

Questions?